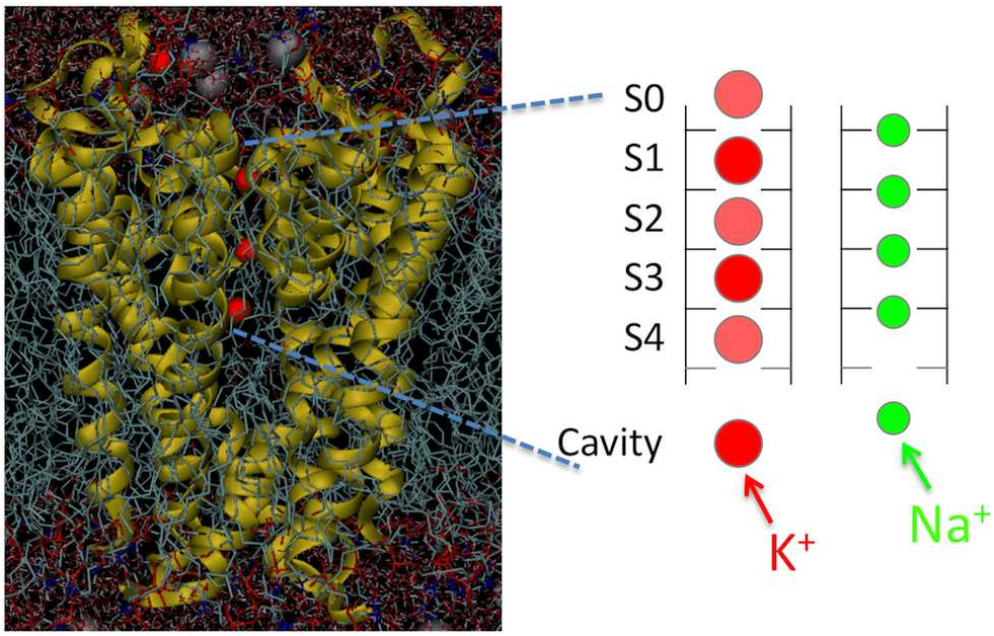
Selective ion binding and its role in potassium channel selectivity

T.W. Allen, Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA, 95616, U.S.A..

Ion channels catalyse rapid and selective ion movement across cell membranes to control electrical and chemical activity in the body. K^+ channels have the remarkable ability to pass K^+ ions at near diffusion-limited rates, while sensitively excluding Na^+ ions; a characteristic essential for membrane repolarization during action potentials. Since it was suggested, over 20 years ago (Neyton & Miller, 1988), that K^+ channel pores consisted of multiple K^+-selective binding sites, and high resolution structures (Doyle *et al.*, 1998; Morais-Cabral *et al.*, 2001) subsequently revealed these sites, the prevailing view has been that K^+ channels select for K^+ ions *via* a mechanism of selective binding.

Recent molecular dynamics simulations (Figure, left), x-ray crystallography and patch clamping (Thompson *et al.*, 2009) have unveiled a putative Na^+ binding site within the K^+ channel selectivity filter, and new calculations (Kim & Allen, 2010) have demonstrated the existence of multiple such sites, leading us to question the hypothesis of selective permeation *via* selective binding. Each K^+ binding site (S0-S4, red balls in the Figure) consists of a cage of 8 carbonyl (or threonine OH for S4) oxygen ligands, made from two planar rings formed by the KcsA tetramer (only two subunits depicted as lines). Each of these sites is adjacent to one or two Na^+ binding sites, consisting of planar rings of 4 carbonyl oxygen atoms, as shown in the Figure (green balls). Free energy calculations indicate that these planar sites select for Na^+ over K^+, and that the net selectivity for K^+ over Na^+ in the selectivity filter is much lower than previously calculated. These results suggest the need for a broader view of selectivity mechanisms, including possible kinetic entry barriers for Na^+ ions (Bezanilla & Armstrong, 1972), with fully-atomistic molecular dynamics simulations helping to reveal those barriers within the multiple-ion permeation process.



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